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Pneumococcal meningitis before the introduction of 10-valent pneumococcal conjugate vaccine into the National Childhood Immunization Program in Poland

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Abstract

Background: Poland introduced the 10-valent conjugate pneumococcal vaccine (PCV10) into the childhood immunization program in January 2017. During previous decades, considerable changes had occurred in the surveillance system for invasive pneumococcal disease. Therefore, to provide baseline data on pneumococcal diseases before PCV10 introduction, we evaluated the epidemiology of pneumococcal meningitis (PM), the only syndrome monitored consistently since 1970.

Methods: Based on laboratory-confirmed cases reported during 2005-2015, we calculated the reported rates, serotypes distribution and antimicrobial resistance of pneumococcal meningitis isolates. Data from the mandatory national surveillance system was linked with data on cerebrospinal fluid isolates submitted to the National Reference Centre for Bacterial Meningitis. We used negative binomial regression with Newey West method to test for trend in rates of pneumococcal meningitis notified during 2005-2015 and Chi-squared test to assess changes in the serotype distribution from 2008-2011 to 2012-2015.

Results: From 2005 to 2015, the overall reported incidence of PM increased from 0.21 to 0.47 cases per 100,000 population, average yearly increase of 7% (rate ratio 1.07; 95% CI 1.06-1.08). The increase was primarily due to annual increase of 3% (1.02-1.05) among 15-49 years of age, 12% (95% CI: 1.10-1.13) among 50-64 years of age, 18% (95% CI: 1.16-1.19) among persons 65-74 years of age and 9% (95%CI 1.07-1.10) among persons ≥75 years of age. In children <5 years of age, serotypes included in PCV10 and PCV13 accounted for 75% and 80% of reported isolates, respectively. From 2008-2011 to 2012-2015, the proportion of PM cases caused by PCV10 serotypes decreased from 52% to 41% ($p<0.01$). Overall, 28% of isolates were resistant to penicillin and 13% were non-susceptible to cefotaxime.

Conclusions: The introduction of PCV10 into national immunization program may have considerable impact on disease burden, especially on number of cases caused by isolates non-susceptible to antimicrobials.

Background

Streptococcus pneumoniae, along with *Neisseria meningitidis* and *Haemophilus influenzae* type b (Hib) [1–4], are most common causes of bacterial meningitis worldwide. In developed countries, case fatality for pneumococcal meningitis (PM) varies from 5% to 20% and sequelae such as hearing loss, seizures or focal neurological deficits occur in up to 50% survivors [1,5–7]. The disease affects mostly young children, the elderly and individuals with chronic illnesses [1]. Due to severity of the condition and established surveillance systems, PM is considered a reliable indicator of *S. pneumoniae* disease burden and long-term trends, allowing for international comparisons [8,9]. Epidemiology of pneumococcal meningitis has changed in many countries after implementation of seven- valent conjugate pneumococcal vaccine (PCV7), which later was replaced by 10- or 13-valent conjugate pneumococcal vaccines (PCV10, PCV13) [10–13]. The treatment of pneumococcal infections is complicated by increasing prevalence of clinical isolates of *S. pneumoniae* that are non-susceptible to first line antibiotics, primarily β-lactams [1,14]. The occurrence of non-susceptibility varies among countries, and may be as high as 40%-80% in certain geographic locations [15–18].

In January 2017, Poland introduced PCV10 into the childhood immunization program. The vaccine is currently administered free of charge in a 2 + 1 schedule at 2, 4 and 13 months of age for children born after 1st January 2017. Before 2017, pneumococcal vaccines (PCV10, PCV13 and the 23-valent polysaccharide vaccine, PPSV23) were given free of charge only to children ≤5 years of age with risk factors. The indications included trauma or defects of central nervous system with cerebrospinal fluid (CSF) leakage, chronic heart failure, immunological-hematological diseases or HIV infection. In addition, some municipalities had organized vaccination at own cost for children registered as residents. In 2015, the vaccine uptake (including children with risk factors receiving any type of pneumococcal vaccine or vaccinated at the cost of their parents) was approximately 10% [19].

Poland introduced mandatory surveillance of PM and other bacterial meningitis in 1970. The system is supervised by two institutions: the National Institute of Public Health- National Institute of Hygiene

(NIPH-NIH) and the reference laboratory - the National Reference Centre for Bacterial Meningitis (NRCBM). In this system, physicians and laboratories report isolations of *S. pneumoniae* from normally sterile sites. In our study, we analyzed baseline data on the epidemiology of pneumococcal meningitis before introduction of PCV10 into the childhood vaccination program in Poland. To provide data for evaluating the impact of PCV10 vaccination program in the future, the specific aims included assessing the reported rates, serotype distribution and antimicrobial resistance of pneumococcal meningitis isolates.

Materials and Methods

Surveillance of pneumococcal meningitis

In Poland, there are two independent passive surveillance systems for monitoring PM. The first system, based on mandatory reporting by physicians, is operated by NIPH-NIH. The second, consisting of voluntary reporting by laboratories is led by NRCBM. In 2005, Poland implemented EU case definition for invasive pneumococcal disease (IPD) and extended the scope of reporting to other manifestations of IPD, than meningitis [20]. Physicians are obliged by law to notify to the local public health authority each suspect IPD case within 24 hours. Microbiological laboratories who isolate *S. pneumoniae* or detect *S. pneumoniae* nucleic acid from normally sterile site from patients also report to the local public health authority. Local public health authorities complete paper-based, standardized surveillance reports for each clinical case of PM and notify it bi-weekly to a population-based surveillance system coordinated by the NIPH-NIH. Multiple notifications with the same identification information (name, surname, address, place of hospitalization) are merged into one case, if they refer to the same illness episode.

Laboratory-based surveillance of PM since 1997 is operated by the NRCBM which receives clinical materials for PCR, the pneumococcal isolates, performs serotyping, and tests antimicrobial susceptibility of isolates. Data on demographic characteristics, antibiotic therapy, vaccination status, clinical symptoms, and the disease outcome, if already available, are collected for all isolates.

Since 2010, data from the NIPH-NIH and the NRCBM have been linked by using identification information and submitted to the European Surveillance System (TESSy) maintained by the European Centre for Disease Prevention and Control (ECDC). Notifications of materials and isolates, which were sent to the NRCBM but not reported to the NIPH, are actively collected as part of an enhanced surveillance. The schematic presentation of surveillance systems of pneumococcal meningitis is depicted in the Graph 1.

Data sources

Data on number of cases, their demographics (age, sex), outcome of the disease and districts where cases were reported, were collected from the population-based surveillance database coordinated by the NIPH-NIH. Year of notification was acquired from the date of onset of symptoms or, if unavailable, specimen collection date. After linkage with the NRCBM databases (based on identification information), data on serotypes and antimicrobial susceptibility of those cases was collected.

Study design

We performed an observational, population-based study. The study population consisted of all residents living in Poland between 1 January 2005 and December 2015.

Case definition

We defined a case of pneumococcal meningitis as isolation of *S. pneumoniae* from CSF during 2005-2015 and notified to the NIP-NIH.

Reported rates and trend

Data were stratified into seven age groups (<1 year, 1-4 years, 5-14 years, 15-49 years, 50-64 years, 65-74 years, ≥75 years). Annual, age-specific and district-specific reported rates per 100,000 were calculated using data from the Central Statistical Office as denominators.

To test trend in rates during 2005-2015 and correct for overdispersion of data, we used negative binomial regression. To adjust for autocorrelation, we used Newey West method. Rate ratios (RR), their 95% confidence intervals (CI) and p-values for yearly changes were calculated using time (year) as a continuous explanatory variable in the model.

Case fatality proportion

We calculated case fatality proportion (CFP) by age group as a number of cases resulting in death, divided by all reported cases. To assess changes in CFP between 2005-2010 and 2011-2015, we used chi-square test; p-value <0.05 was considered statistically significant.

Serotype distribution and diversity

We calculated proportions of *S. pneumoniae* isolates by vaccine- serotypes. The 10-valent pneumococcal conjugate vaccine contains serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F; the 13-valent pneumococcal conjugate vaccine adds serotypes 3, 6A, and 19A. Those three additional serotypes were defined as PCV13 - PCV10. The 23-valent pneumococcal polysaccharide vaccine contains 12 serotypes in common with PCV13 and 11 unique serotypes (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F). The non-vaccine types were categorized as non-PCV10 and non-PCV13. Serotypes 15B and 15C were grouped together as 15B/C because of the reported reversible switching between these serotypes, which makes differentiation difficult [21]. We used chi-squared test to assess changes in the serotype distribution between 2008-2011 and 2012-2015.

To assess the diversity of reported serotypes, we used the Simpson's index of diversity (D) [22]. D refers to the probability that two randomly selected isolates have different serotypes. We defined D as:

$$D = \frac{N}{(N-1)} \times \left[1 - \sum_{i=1}^{m} \left(\frac{n_i}{N}\right)^2\right]$$

where, N is the total number of pneumococcal meningitis cases (sample size), n is the number of cases with serotype i, m is the total number of serotypes [23].

Serotyping

S. pneumoniae CSF isolates sent to the NRCBM were serotyped using Pneumotest-Latex kit (Statens Serum Institut, Copenhagen, Denmark), PCR or sequencing. Serotypes not identified by the above methods were subjected to the Neufeld Quellung test in the Statens Serum Institut in 2008, and in the National Reference Center for Streptococci in Aachen, Germany in 2009-2015, as previously described [24].

Antimicrobial susceptibility

Minimal inhibitory concentrations (MICs) for penicillin and cefotaxime were determined by the Etest (AB Biodisk-bioMérieux) or MICEvaluators (Oxoid-Thermo Fisher) according to manufactures instructions.

For the interpretation of MICs data, the EUCAST 2015 breakpoints for meningitis cases were applied [25]. Pneumococcal meningitis isolates were categorized as susceptible (S), intermediate (I), and resistant (R). The intermediate and resistant isolates were collectively referred to as non-susceptible.

Data analysis

All analyses were done with STATA version 13 (STATA Corp., Texas, USA) and Microsoft Excel 2013.

Ethical considerations

Data used in the analysis were collected as a part of national routine surveillance activities which fall under the existing mandate of the NIPH-NIH and the NRCBM. No formal approval of Institutional Review Board was required for this non-interventional study [26]. Identification data (names, addresses) were removed after matching with vital status or serotype.

Results

Descriptive analysis

From January 2005 until December 2015, a total of 1435 cases of pneumococcal meningitis were notified to the NIPH-NIH. Information on age was available for 1432 (99.8%) cases. The median age of cases was 48 years (interquartile range (IQR), 25-60 years), and 63% (910/1435) were male. Fourteen percent (200/1432) of cases were in children under 5 years of age and 16% (226/1432) were adults ≥ 65 years. The overall case fatality proportion was 20% (281 deaths) and varied from 4% (4/90) in children under 1 year of age to 31% (71/226) in people ≥ 65 years of age. Most of the deaths occurred within 30 days of symptom onset (81%, 228/281). The CFP was higher in 2005-2010 (22%) than in 2011-2015 (18%) (p=0.052).

Reported rates of pneumococcal meningitis and trends

The highest rate was among children under 1 year of age, followed by 1-4 years of age and people 65-74 years of age (Table 1). The reported rates in the youngest age group were characterized by substantial variation, from 0.52 cases per 100,000 person-years in 2007 to 3.59 cases per 100,000 person-years in 2010. The overall rate increased steadily from 0.21 cases per 100,000 person-years in 2005 to 0.47 cases per 100,000 person-years in 2015. This represented an average increase by 7% per year (RR 1.07, 95% CI: 1.06-1.08), primarily due to annual increase by 3% (1.02-1.05) among 15-49 years of age, 12% (95% CI: 1.10-1.13) among 50-64 years of age, 18% (95% CI: 1.16-1.19) among persons 65-74 years of age and 9% (95%CI 1.07-1.10) among ≥75 years of age. Trends in other age groups were not statistically significant (Table 1). Male to female rate ratio was 1.85 (0.45 cases/100,000 person-years vs. 0.24 cases/100,000 person-years). There were geographical differences in the reported rates notified in 2005-2015, ranging from 0.18 cases per 100,000 person-years in district 10, to 0.52 cases per 100,000 person-years in district 11 (Figure 1). The reported rate was higher in urban areas, than rural (0.38 cases per 100,000 person-years and 0.28 cases per 100,000 person-years, respectively).

Serotype distribution of pneumococcal meningitis isolates

Of the 1149 PM cases reported to the NIPH-NIH in 2008-2015, 676 (59%) CSF isolates were sent to the NRCBM. The proportion of isolates sent to the NRCBM varied from 49% in 2008 to 67% in 2015. Of the 676 isolates available for serotyping, 672 belonged to 48 different serotypes or serogroups; 4 isolates were non-typeable. The most common serotypes were 3 (71 isolates, 11% of all isolates), 19F (65, 10%), 14 (58, 9%) and 23F (40, 6%). There were no significant differences in serotype distribution between 2008-2011 and 2012-2015, except an increase in serotype 19A (increase from 2% in 2008-2011 to 6% in 2012-2015, p= 0.0106) and 23B (from 0% to 3%, p= 0.0027). The serotypes present in PCV10, PCV13 and PPSV23 accounted for 46% (309/676), 62% (419/676) and 83% (563/676) of all isolates, respectively. Between 2008-2011 and 2012-2015, there was significant decrease in the proportion of cases caused by PCV10 serotypes, from 52% to 41% (p= 0.0044), respectively. There were no significant changes in proportions of PCV13 (p= 0.0630) and PPSV23 (p= 0.0848), PCV13-PCV10 (p= 0.1622) and PPSV23 unique serotypes (p= 0.5409).

Among serotypes identified at least 20 times during the study period, the highest CFP was found for serotype 4 (34%, 12 deaths/35 isolates), 8 (29%, 6/21), 22F (29%, 6/21) and 10A (22%, 5/23). However, the observed differences in CFPs were not statistically significant.

Of the 112 isolates notified in children under 5 years of age, most common were serotypes 14 (n=23, 21%), 19F (n=22, 20%), 6B (n=14, 13%), 23F (n=9, 8%), 9V (n=6, 5%) and 15B/C (n=5, 5%) (Table 2). There were no significant changes in frequency of particular serotypes between 2008-2011 and 2012-2015. PCV10, PCV13 and PPSV23 serotypes accounted for 75% (84/112), 80% (90/112) and 93% (104/112) of isolates, respectively. Comparing the distribution of serotypes in 2008-2011 to 2012-2015, the proportion of PCV10 serotypes declined from 87% to 57% (p= 0.0004); PCV13 serotypes decreased from 91% to 64% (p= 0.0003), PPSV23 serotypes decreased from 96% to 89% (p= 0.1511) and the proportion of non-PCV10 serotypes increased from 13% to 43% (p= 0.0004), non-PCV13 from 9% to 36% (p= 0.0003) and PCV13-PCV10 serotypes from 4% to 7% (p= 0.4860).

Among individuals ≥5 years of age (564 isolates), the most common were serotypes 3 (n=70, 12%), 19F (n=43, 8%), 14 (n=35, 6%), 4 (n=33, 6%), 23F (n=31, 6%) and 19A (n=27, 5%) (Table 3). PCV10, PCV13 and PPSV23 serotypes accounted for 40% (225/564), 58% (329/564) and 81% (459/564) of isolates, respectively. There were no significant changes in proportion of PCV10, PCV13 or non-PCV10, non-PCV13 and PCV13-PCV10 serotypes between 2008-2011 and 2012-2015.
Simpson's index of diversity was 0.894 and 0.954 in children < 5 years of age and individuals ≥5 years, respectively.

Antimicrobial susceptibility

Data for antimicrobial susceptibility were available for 670 pneumococcal meningitis isolates (99.1%) reported in 2008-2015. Overall, 28% (189/669) of isolates were resistant to penicillin (MIC >0.06 mg/L). There was no significant change in the frequency of penicillin resistant isolates reported in 2008-2011 and 2012-2015 (29% and 27% respectively, p = 0.5671). Resistance to penicillin was common among serotypes 19A (26/29, 90%), 9V (19/24, 79%), 19F (47/65, 72%), 14 (40/58, 69%) and 6B (23/35, 66%). Among children <5 years of age, 53% (58/110) of the isolates were resistant to penicillin compared with 23% among persons $\geq$ 5 years of age (p<0.0001). Serotypes with high proportion of penicillin resistance were: 19A (2/2, 100%), 9V (6/6, 100%), 23B (1/1, 100%), 19F (18/22, 82%), 14 (16/23, 70%), 6A (2/3, 67%) and 23F (5/9, 56%).
Isolates with decreased susceptibility to cefotaxime (MIC >0.5 mg/L) constituted 13% (90/670) of isolates tested in 2008-2015. The frequency of cefotaxime non-susceptibility did not change significantly between 2008-2011 (14%) and 2012-2015 (13%) (p = 0.7066). Non-susceptibility to cefotaxime was highest among isolates of serotypes 19A (17/29, 59%), 35B (1/2, 50%), 19F (30/65, 46%), 14 (25/58, 43%), 23F (10/40, 25%) and 9V (5/24, 21%). Among children < 5 years of age, 22% (24/110) of isolates were non-susceptible to cefotaxime compared with 12% among persons $\geq$5 years of age (p = 0.0052). The highest proportion of cefotaxime non-susceptible isolates was identified in serotypes 19A (2/2, 100%), 23 F (4/9, 44%), 14 (10/23, 43%) and 19F (8/22, 36%).

Discussion

Our study described comprehensive 10-year baseline epidemiologic characteristics of PM cases reported to the national surveillance system (NIPH-NIH) in Poland before the introduction of universal PCV10 vaccination. To date, the analysis of epidemiology of PM was conducted only by the NRCBM and was limited to submitted isolates. There was an increasing trend in reported rates of pneumococcal meningitis, primarily among persons older than 15 years. During the study period almost half of the cases were caused by PCV10 serotypes. The average penicillin resistance of isolates was significantly higher among children less than 5 years of age and higher than in most European countries.

The age distribution of reported cases in Poland was similar to that notified in other European countries, with children below 5 years of age and persons $\geq$ 65 years of age having highest reported rates. Although the rates observed in our study (average 0.34 cases per 100,000 person-years) were higher than in the previous Polish studies [27,28], the overall and age-specific rates were considerably lower than those reported from other countries before introduction of pneumococcal conjugate vaccines, such as Finland [29], the Netherlands [30], England and Wales [31], Austria [32] or USA [10]. The low rates for pneumococcal meningitis in Poland may be due to low surveillance sensitivity or frequent administration of antibiotics immediately after clinical diagnosis or suspicion of meningitis, resulting in negative culture results [28]. The largest differences in reported rates between Poland and other European countries were among the elderly, suggesting considerable underreporting in this age group. This hypothesis is supported by the findings from the prospective study conducted in 124 pediatric hospitals or wards in five randomly selected districts in Poland during 2003-2004 [33]. The rates of pneumococcal meningitis were estimated to be 3.8 cases/ 100,000 person-years in children < 5 years of age and 4.1 in children <2 years of age, respectively. The study showed that 108 out of 134 cases of laboratory-confirmed invasive pneumococcal disease were culture-negative and therefore serotyping data was available for 26 isolates only. Additionally,

28% children were treated with antibiotics before blood or CSF sampling. Relatively low reported rates should be taken into account when designing future vaccine effectiveness or impact studies or conducting evaluations of the economic and health benefits of the PCV10 vaccination program. Underestimated burden of meningitis will affect the absolute number of cases prevented/reduced after conjugate vaccine introduction.

The increasing rates of pneumococcal meningitis from 0.21 cases per 100,000 person-years in 2005 to 0.47 cases per 100,000 person-years in 2015 may reflect changes and systematic improvements in the surveillance system for IPD. Historically, epidemiological surveillance of IPD in Poland was limited to meningitis cases, which have been routinely reported by physicians since 1970. The implementation of EU case definition for IPD in 2005 [20], allowed collection of data on whole spectrum of clinical manifestations of IPD and thus improved surveillance sensitivity. In addition, active searching of cases reported to the NRCBM but not reported to the NIPH, increased the number of reported cases included in the national surveillance data. The significant increase in rate was reported primarily among persons $\geq$15 years of age. This may be related to better case ascertainment and reporting in this age group. However, influence of secular trends cannot be excluded. The reason for the substantial variation in reported rates in children <1 years of age, between 2007 (0.5 cases per 100,000 person-years) and 2010 (3.59 cases per 100,000 person-years) is unknown, since there were no outbreaks reported. During the study period, changes in reported rates among children < 15 years of age were not statistically significant. This might be related to small number of cases, fluctuations in reported rates which affect the possibility to observe linear trend, or to other factors.

Changes in clinical practice also might have influenced the increased number of observed cases. However, in Poland, as in most European countries, cerebrospinal fluid (CSF) collection is a standard procedure in suspected pneumococcal meningitis [34]. Thus, epidemiology of PM is likely to be less

affected by changes in clinical practice than IPD incidence where blood culturing practices for diagnosis of pneumonia can influence observed rates [9,35]. Taking into account changes in surveillance system, the data on observed trends should be interpreted with caution.

The observed lower CFP in 2011-2015 comparing to 2005-2010, might be related to better surveillance, since more cases with less severe disease could have been reported. In addition in 2011, the national guidelines for diagnostic and treatment of bacterial meningitis were edited under umbrella of the National Programme for Antibiotic Protection by the National Medicines Institute [34].

The serotype distribution of pneumococcal meningitis isolates was characterized by considerable heterogeneity, especially among persons ≥5 years of age. Higher heterogeneity in older age groups has also been observed in other countries [36]. As in other countries before implementation of vaccination, the most common serotypes in children were 14, 19F, 23F [37,38]. In adults, serotype 3 was most common. Findings from other studies indicated that serotype 3 is commonly isolated in meningitis and associated with unfavorable outcomes [39]. The highest CFPs were reported for serotypes 4, 8, 22F and 10A. In a Danish nationwide population-based study, serotypes 4, 8, 22F were also found to be associated with higher 30-day mortality in meningitis patients [40]. There was significant increase in the proportion of serotype 19A and 23B reported in 2012-2015, compared with 2008-2011. In children < 5 years of age, the most common were serotypes 14 and 19F. Both serotypes are targeted by available vaccines. In children <5 years of age, serotypes targeted by PCV10 and PCV13 accounted for higher proportion of all reported isolates, than in individuals ≥5 years of age. However, in children < 5 years of age, proportion of PCV10 and PCV13 serotypes decreased significantly from 2012-2015 to 2008-2010. It is difficult to assess the impact of local vaccination programs on the rise in non-PCV serotypes, because detailed data on vaccine coverage in

specific time and regions were unavailable. These results indicate high potential for prevention of meningitis cases by PCV10, PCV13 and PPSV23 vaccines.

A number of studies have documented a significant decline in the reported rates of PM in the PCV vaccinated children. Some studies have shown the decrease in incidence also in older children and adults not targeted by vaccine, through herd effect. However, decrease in incidence due to the vaccine serotypes resulted in an increase in PM caused by non-vaccine serotypes [23]. In countries where PCV7 or PCV10 has been used in the infant vaccination programs, number of serotype 19A cases has increased both in children and adults, becoming one of the most common cause of meningitis. In contrast, after implementation of infant PCV13, the number of serotype 19A cases decreased significantly among both vaccinated and unvaccinated population groups [41]. However, increases in proportion of a wide variety of non-PCV13 serotypes have been seen after PCV13 introduction. In Germany, a significant increase in percentage of serotypes 12F, 15C, 22F, 23B and 35B was observed in children, after PCV introduction. In adults, increases in percentage of serotypes 6C, 12F, 15B, 22F, 23A, 23B and 35B were observed [42]. In France, after PCV13 introduction increase in frequency of serotypes 12F, 24F, 23B, 10A, 15A and 6C was observed [43]. However, results of herd effect and serotype replacement were not consistent in all countries. To allow assessment of changes in serotype distribution and potential serotype replacement in Poland, ongoing surveillance on circulating strains is essential.

The average penicillin resistance of isolates amounted 28% and was significantly higher among children less than 5 years of age. There were no substantial changes in penicillin resistance during the study period. Poland along with Romania, Malta and Iceland, has one of the highest proportion of IPD isolates resistant to penicillin. In Europe there is wide variation in antimicrobial susceptibility of pneumococcal isolates [44]. Differences are likely related to diversity in circulating strains, antibiotic use, vaccination policy, diagnostic capacity and access to healthcare. In our study, most of

penicillin resistant isolates were targeted by PCV13. Several studies have demonstrated that vaccination with pneumococcal conjugate vaccines (PCV7, PCV10 and PCV13) reduced the nasopharyngeal carriage of penicillin-resistant *S. pneumoniae* and thus pneumococcal resistance in vaccinated and unvaccinated population [45–47]. Prevention is especially important since antimicrobial resistance has been associated with worse clinical outcomes in patients with pneumococcal meningitis [48].

In addition to low sensitivity, the surveillance system for pneumococcal meningitis in Poland has several other limitations. Our study shows substantial regional variation in reported rates. This suggests considerable underreporting in some districts (district 10, 3, 6, 13) and important areas for improvement. In addition, during 2008-2015 less than 60% of isolates reported to the NIPH-NIH were sent to the NRCBM and serotyped. Formal evaluation of the surveillance system should be performed before conducting vaccine effectiveness or impact studies. This is especially important because of the planned change from paper-based to electronic based reporting surveillance system. Changes in surveillance can affect sensitivity of surveillance and quality of surveillance data. Media attention for pneumococcal disease after introduction of PCV10 could possibly improve awareness of IPD and result in further increase in the number of reported cases.

The strength of the study is a population-based design and all residents are entitled to free acute healthcare. Pneumococcal meningitis is a severe and life-threatening condition, thus each case is hospitalized. However, several limitations of this study should be noted. In the analysis only CSF culture-confirmed cases were included. Cases diagnosed on the basis of other laboratory methods such as PCR or antigen detection from CSF or blood culture with clinical symptoms of meningitis, were excluded from the study. This may have led to underestimation of the number of cases. The trend in reported rates was probably affected by the matching of cases captured by the two surveillance systems, initiated in 2010. However, the separate analysis of cases passively reported

only was not possible due to lack of register of actively collected cases in 2010-2014, and thus different form of reporting. Since the outcome of the disease was collected by the public health authority, there is a possibility that some fatal cases were not captured, if the death occurred after the collection of the data or the patients was moved to another hospital.

Conclusions

This is the first study assessing long term trends of pneumococcal meningitis cases reported to mandatory surveillance system in Poland. The reported incidence of pneumococcal meningitis increased in persons ≥15 years of age. In children <5 years of age, serotypes included in PCV10 and PCV13 accounted for 75% and 80% of reported isolates, respectively. The introduction of PCV10 into national immunization program may have considerable impact on disease burden, especially on number of cases caused by isolates non-susceptible to antimicrobials.

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Conflict of interest statement

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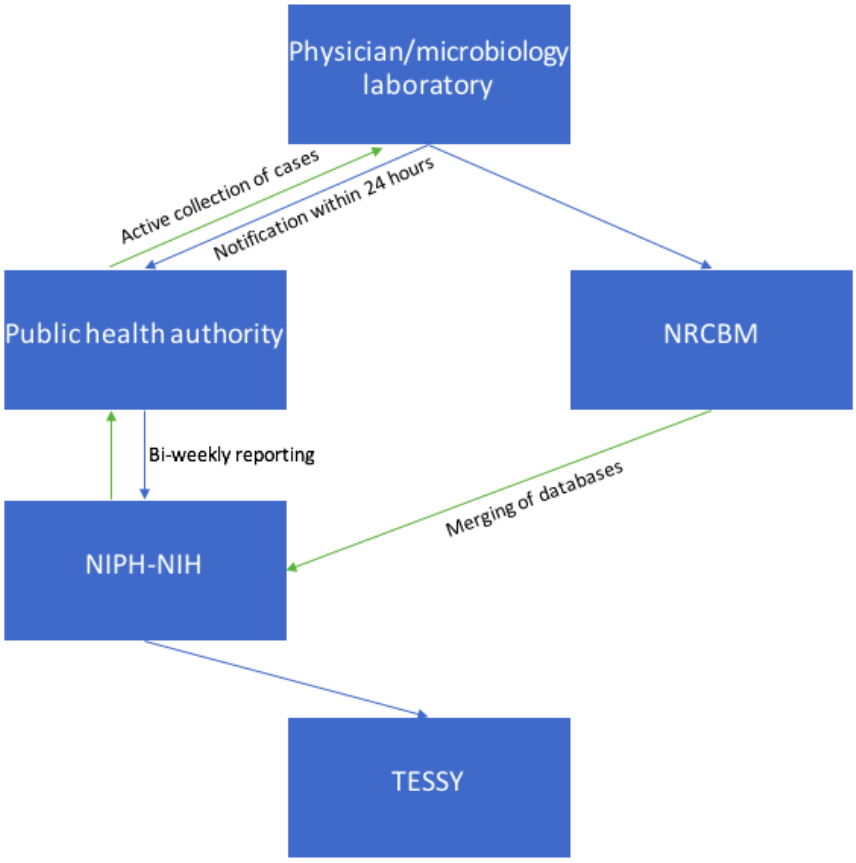
Graph 1. Surveillance system of pneumococcal meningitis in Poland



NRCBM- National Reference Centre for Bacterial Meningitis; NIPH-NIH- National Institute of Public Health- National Institute of Hygiene; TESSy- The European Surveillance System.

Blue line- standard surveillance; Green line- Enhanced surveillance

Table 1. Rates and number of cases of pneumococcal meningitis according to age group (years) and mean annual relative change in incidence, 2005-2015, Finland

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2005-2015	% Change* (95%CI)
<1	1.94 (7)	1.64 (6)	0.52 (2)	1.94 (8)	2.12 (9)	3.59 (15)	2.77 (11)	1.56 (6)	3.26 (12)	2.18 (8)	1.66 (6)	2.12 (90)	4 (-2 to 10)
1-4	0.35 (5)	0.56 (8)	0.77 (11)	0.68 (10)	0.53 (8)	0.77 (12)	1.20 (20)	0.60 (10)	0.36 (6)	0.45 (7)	0.85 (13)	0.65 (110)	3 (-1 to 8)
5-14	0.24 (11)	0.14 (6)	0.29 (12)	0.25 (10)	0.31 (12)	0.21 (8)	0.29 (11)	0.13 (5)	0.27 (10)	0.26 (10)	0.21 (8)	0.24 (103)	-1 (-3- to 0)
15-49	0.14 (27)	0.18 (35)	0.26 (51)	0.20 (38)	0.24 (47)	0.23 (44)	0.22 (42)	0.16 (30)	0.32 (60)	0.20 (38)	0.29 (54)	0.22 (466)	3 (2 to 5)
50-64	0.32 (22)	0.34 (24)	0.29 (22)	0.40 (31)	0.40 (31)	0.46 (37)	0.69 (57)	0.47 (39)	0.67 (55)	0.77 (62)	0.72 (57)	0.51 (437)	12 (10 to 13)
65-74	0.20 (6)	0.17 (5)	0.32 (9)	0.22 (6)	0.54 (15)	0.44 (12)	0.33 (9)	0.53 (15)	0.94 (28)	0.47 (15)	0.92 (31)	0.47 (151)	18 (16 to 19)
≥75	0.14 (3)	0.27 (6)	0.30 (7)	0.13 (3)	0.34 (8)	0.20 (5)	0.28 (7)	0.35 (9)	0.31 (8)	0.34 (9)	0.37 (10)	0.28 (75)	9 (7 to 10)
TOTAL	0.21 (81)	0.24 (90)	0.30 (114)	0.28 (106)	0.34 (130)	0.35 (133)	0.41 (157)	0.30 (114)	0.46 (179)	0.39 (149)	0.47 (179)	0.34 (1432)	7 (6 to 8)

* Mean annual relative change in incidence calculated by negative binomial regression with Newey West method

Table 2. Serotypes distribution (%) of pneumococcal meningitis isolates among persons <5 years of age reported to the NIP-NIH, 2008-2015, Poland

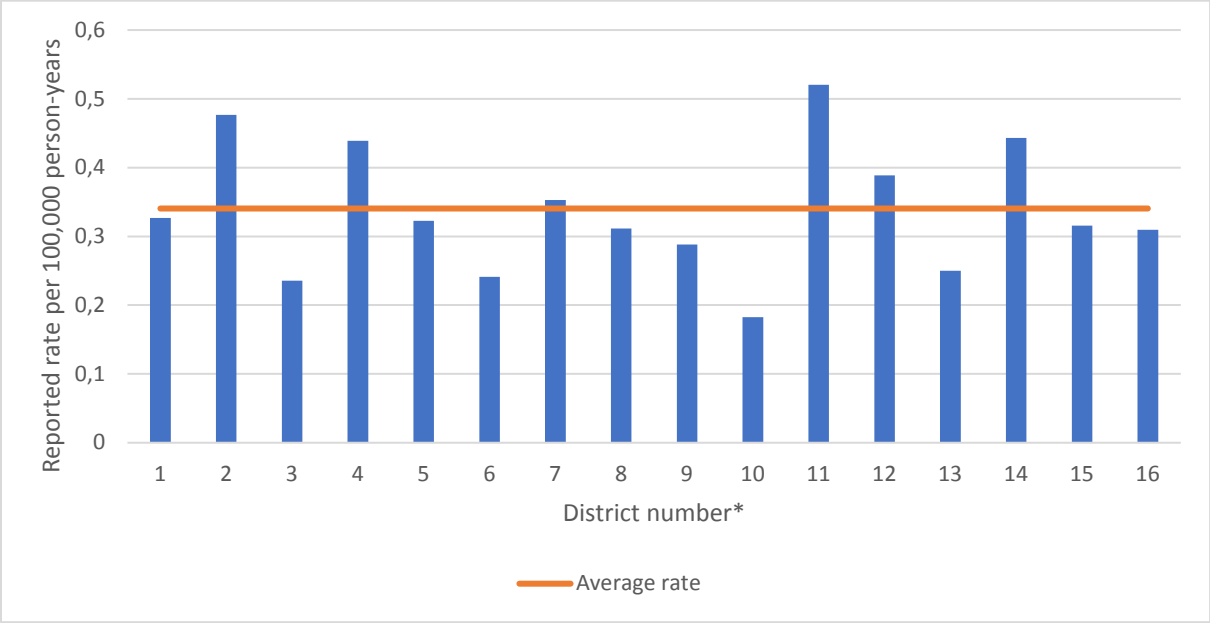
	2008	2009	2010	2011	2012	2013	2014	2015	2008-2015
NO. OF CASES REPORTED TO THE NIP-NIH	18	17	27	31	16	18	15	19	161
NO. AND PROPORTION (%) OF ISOLATES SENT TO THE NRCBM AND SEROTYPED	15 (83)	13 (76)	19 (70)	21 (68)	9 (56)	13 (72)	10 (67)	12 (63)	112 (67)
NO. OF DIFFERENT SEROTYPES	8	6	7	8	9	9	8	8	25
SIMPSON D' INDEX	0.914	0.821	0.860	0.838	1.000	0.923	0.956	0.939	0.894
PCV10/PCV13 SEROTYPES									
1	0.0	0.0	0.0	0.0	0.0	7.7	0.0	0.0	0.9
4	0.0	0.0	0.0	4.8	0.0	0.0	10.0	0.0	1.8
5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
6B	20.0	7.7	21.1	9.5	11.1	7.7	0.0	16.7	12.5
7F	13.3	7.7	0.0	0.0	0.0	0.0	0.0	0.0	2.7
9V	0.0	0.0	5.3	19.0	11.1	0.0	0.0	0.0	5.4
14	13.3	23.1	26.3	33.3	0.0	23.1	20.0	8.3	20.5
18C	6.7	15.4	0.0	0.0	11.1	0.0	0.0	0.0	3.6
19F	6.7	38.5	21.1	19.0	11.1	23.1	20.0	16.7	19.6
23F	20.0	0.0	10.5	4.8	11.1	7.7	10.0	0.0	8.0
ADDITIONAL PCV13 SEROTYPES									
3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8.3	0.9
6A	0.0	7.7	10.5	0.0	0.0	0.0	0.0	0.0	2.7
19A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	16.7	1.8
OTHER SEROTYPES									
15B/C	13.3	0.0	0.0	0.0	11.1	0.0	0.0	16.7	4.5
10A	0.0	0.0	5.3	4.8	11.1	7.7	0.0	0.0	3.6
8	0.0	0.0	0.0	0.0	0.0	7.7	0.0	8.3	1.8
22F	6.7	0.0	0.0	0.0	0.0	0.0	0.0	8.3	1.8
11A	0.0	0.0	0.0	4.8	0.0	0.0	0.0	0.0	0.9
12F	0.0	0.0	0.0	0.0	11.1	0.0	0.0	0.0	0.9
33F	0.0	0.0	0.0	0.0	0.0	0.0	10.0	0.0	0.9
9N	0.0	0.0	0.0	0.0	0.0	0.0	10.0	0.0	0.9
27	0.0	0.0	0.0	0.0	0.0	0.0	10.0	0.0	0.9
38	0.0	0.0	0.0	0.0	0.0	0.0	10.0	0.0	0.9
23B	0.0	0.0	0.0	0.0	0.0	7.7	0.0	0.0	0.9
24F	0.0	0.0	0.0	0.0	0.0	7.7	0.0	0.0	0.9
35F	0.0	0.0	0.0	0.0	11.1	0.0	0.0	0.0	0.9
PERCENTAGE OF ALL ISOLATES									
PCV10 SEROTYPES	80.0	92.3	84.2	90.5	55.6	69.2	60.0	41.7	75.0
NON-PCV10 SEROTYPES	20.0	7.7	15.8	9.5	44.4	30.8	40.0	58.3	25.0
PCV13 SEROTYPES	80.0	100.0	94.7	90.5	55.6	69.2	60.0	66.7	80.4
PCV13-PCV10 SEROTYPES	0.0	7.7	10.5	0.0	0.0	0.0	0.0	25.0	5.4
NON-PCV13 SEROTYPES	20.0	0.0	5.3	9.5	44.4	30.8	40.0	33.3	19.6
PPSV23 SEROTYPES	100.0	92.3	89.5	100.0	88.9	84.6	80.0	100.0	92.9
PPSV23 UNIQUE SEROTYPES	20.0	0.0	5.3	9.5	33.3	15.4	20.0	33.3	15.2
NON-PPSV23 SEROTYPES	0.0	0.0	0.0	0.0	11.1	15.4	20.0	0.0	4.5

Table 3. Serotypes distribution (%) of pneumococcal meningitis isolates among persons ≥5 years of age reported to the NIPH-NIH, 2008-2015, Poland

	2008	2009	2010	2011	2012	2013	2014	2015	2008-2015
NO. OF CASES REPORTED TO THE NIP-NIH	88	113	106	126	98	161	134	160	986
NO. OF ISOLATES (%) SENT TO NRCBM AND SEROTYPED	37 (42)	66 (58)	66 (62)	59 (47)	57 (58)	96 (60)	90 (67)	93 (58)	564 (57)
NO. OF DIFFERENT SEROTYPES	20	31	26	28	21	32	28	31	49
SIMPSON D' INDEX	0.961	0.962	0.947	0.943	0.949	0.960	0.943	0.963	0.954
PCV10/PCV13 SEROTYPES									
1	0.0	0.0	1.5	1.7	0.0	2.1	1.1	2.2	1.2
4	5.4	6.1	7.6	3.4	7.0	6.3	6.7	4.3	5.9
5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
6B	5.4	1.5	3.0	6.8	3.5	4.2	5.6	2.2	3.9
7F	2.7	0.0	1.5	3.4	0.0	2.1	5.6	0.0	2.0
9V	8.1	3.0	3.0	1.7	1.8	5.2	1.1	3.2	3.2
14	8.1	6.1	9.1	3.4	5.3	5.2	6.7	6.5	6.2
18C	2.7	6.1	7.6	3.4	8.8	5.2	1.1	2.2	4.4
19F	10.8	3.0	13.6	6.8	10.5	7.3	5.6	6.5	7.6
23F	5.4	3.0	7.6	5.1	8.8	6.3	3.3	5.4	5.5
ADDITIONAL PCV13 SEROTYPES									
3	10.8	10.6	10.6	20.3	12.3	9.4	17.8	8.6	12.4
6A	0.0	1.5	1.5	0.0	1.8	2.1	0.0	2.2	1.2
19A	2.7	1.5	1.5	6.8	3.5	8.3	6.7	4.3	4.8
OTHER SEROTYPES									
8	8.1	1.5	3.0	1.7	5.3	2.1	2.2	5.4	3.4
10A	5.4	3.0	3.0	0.0	5.3	1.0	2.2	7.5	3.4
22F	0.0	1.5	3.0	3.4	7.0	1.0	4.4	5.4	3.4
9N	2.7	4.5	1.5	1.7	1.8	4.2	2.2	4.3	3.0
11A	2.7	3.0	6.1	3.4	0.0	3.1	3.3	1.1	2.8
15B/C	5.4	3.0	0.0	5.1	3.5	5.2	0.0	2.2	2.8
12F	2.7	12.1	0.0	1.7	1.8	1.0	1.1	2.2	2.7
17F	0.0	1.5	0.0	1.7	3.5	0.0	0.0	0.0	0.7
33F	0.0	0.0	0.0	1.7	1.8	0.0	1.1	0.0	0.5
20	2.7	3.0	1.5	0.0	3.5	0.0	2.2	0.0	1.4
2	0.0	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.2
23A	2.7	1.5	0.0	0.0	0.0	3.1	3.3	5.4	2.3
23B	0.0	0.0	0.0	0.0	0.0	2.1	5.6	5.4	2.1
6C	0.0	3.0	0.0	1.7	0.0	1.0	3.3	2.2	1.6
15A	0.0	1.5	1.5	1.7	1.8	1.0	1.1	1.1	1.2
6A	0.0	1.5	1.5	0.0	1.8	2.1	0.0	2.2	1.2
31	0.0	3.0	0.0	1.7	0.0	1.0	0.0	1.1	0.9
OTHER**	5.4	12.1	10.6	11.9	0.0	8.3	6.7	7.5	8.0
PERCENTAGE OF ALL ISOLATES									
PCV10 SEROTYPES	48.6	28.8	54.5	35.6	45.6	43.8	36.7	32.3	39.9
NON-PCV10 SEROTYPES	51.4	71.2	45.5	64.4	54.4	56.3	63.3	67.7	60.1
PCV13 SEROTYPES	62.2	42.4	68.2	62.7	63.2	63.5	61.1	47.3	58.3
PCV13-10 SEROTYPES	13.5	13.6	13.6	27.1	17.5	19.8	24.4	15.1	18.4
NON-PCV13 SEROTYPES	37.8	57.6	31.8	37.3	36.8	36.5	38.9	52.7	41.7
PPSV23 SEROTYPES	91.9	75.8	84.8	83.1	94.7	79.2	80.0	73.1	81.4
PPSV23 UNIQUE SEROTYPES	29.7	34.8	18.2	20.3	33.3	17.7	18.9	28.0	24.3
NON-PPSV23 SEROTYPES	8.1	24.2	15.2	16.9	5.3	20.8	20.0	26.9	18.6

**Serotypes other than presented in the table, that occurred less than 10 times in 2005-2015 in Poland. Non-typeable isolates (n=4) were included.

Fig. 1 Reported rate of pneumococcal meningitis by district, Poland, 2005-2015



*1- Dolnośląskie, 2- Kujawsko-pomorskie, 3- Lubelskie, 4- Lubuskie, 5- Łódzkie, 6- Małopolskie, 7- Mazowieckie, 8- Opolskie, 9- Podkarpackie, 10- Podlaskie, 11- Pomorskie, 12- Śląskie, 13- Świętokrzyskie, 14- Warmińsko-mazurskie, 15- Wielkopolskie, 16- Zachodniopomorskie